UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JEFFREY T. BLUE

Appeal 2007-4454
Application 10/030,378
Technology Center 1600

Decided: November 6, 2007

Before ERIC B. GRIMES, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-8 and 18-25. We have jurisdiction under 35 U.S.C. § 6(b). Claim 1 is representative of the claims on appeal, and reads as follows:

1. A method for assaying activity of a virus to determine viral stability and potency comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus obtained from a first formulation, wherein said virus induces caspase 3 activity; and

(b) measuring said caspase 3 activity as an indication of virus activity,

wherein said steps (a) and (b) are repeated with either: (i) said virus taken from a second formulation, said second formulation being different than said first formulation, and the difference in caspase 3 activity from said virus taken from said first and second formulation provides an indication of virus stability and potency in said first formulation compared to said second formulation; or (ii) said virus taken from said first formulation at two or more time intervals and the difference in caspase 3 activity between said two or more time intervals provides an indication of virus stability and potency in said first formulation.

The Examiner relies on the following references:

Goodrich, Jr. (Goodrich)	US 5,958,670	Sep. 28, 1999
Wu	US 6,689,600 B1	Feb. 10, 2004

Esolen *et al.*, "Apoptosis as a Cause of Death in Measles Virus-Infected Cells," *Journal of Virology*, Vol. 69, No. 6, pp. 3955-3958 (June 1995).

Banki *et al.*, "Molecular Ordering in HIV-induced Apoptosis," *The Journal of Biological Chemistry*, Vol. 273, No. 19, pp. 11944-11953 (May 1998).

Duncan *et al.*, "Rubella Virus-Induced Apoptosis Varies among Cell Lines and Is Modulated by Bcl-X_L and Caspase Inhibitors," *Virology*, Vol. 255, pp. 117-128 (1999).

We affirm.

BACKGROUND

According to the Specification, "[v]iral induction of caspase 3 activity was found to provide a reliable measure of viral activity." (Specification 1.)

"[C]aspase 3 activity induced by viral infection can be measured using techniques well known in the art." (*Id.* at 4.)

The major group of effector caspases is exemplified by caspase 3 (Duncan, p. 123, first column). "Caspase 3 (also known as CPP32 or apopain) is a member of the caspase family of proteases. Caspases are induced by apoptosis, which is an active process of cellular suicide. Apoptosis has been indicated to be induced by different stimuli including infection by different viruses." (Specification 3-4 (references omitted).)

DISCUSSION

Claims 1-3 and 7 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Banki. As Appellants do not argue the claims separately, we focus our analysis on independent claim 1. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

Banki is cited for teaching a method of measuring caspase activity as required by claim 1 (Answer 5). The Examiner relies on page 11947, Caspase-3/CPP32 Enzyme Assay and Protease Inhibitors section, and the caption of Figure 2 for repeating steps a) and b) at two or more time intervals (Answer 11-12).

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *See In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). We find that Banki in fact anticipates the subject matter of claim 1, and the rejection is affirmed.

Claim 1 requires the steps of:

a) contacting a plurality of cells susceptible to caspase 3 induction with a virus from a first formulation;
b) measuring caspase 3 activity; and
c) when using only one formulation, repeating the first two steps, with said virus being taken from said formulation at two or more time intervals.

Banki teaches an enzyme assay for caspase 3 comprising incubating cells susceptible to caspase 3 induction (H9 and Jurkat-tat cells) (Banki, p. 11949, Figure 2, legend) with a fluorescent substrate (Banki, p. 11947, paragraph bridging columns 1 and 2) after infection with HIV-1 DNA clone 4803 (Banki, p. 11947, first column; p. 11948, second column). The legend of Figure 2 states that caspase 3 activity "was measured by cleavage of DEVD-AFC using extracts of H9 (E) and Jurkat-tat cells (F) undergoing HIV induced apoptosis." The data presented as panels (E) and (F) of Figure 2 represent the mean of four or more independent experiments.

Thus, both the Examiner and Appellant agree that Banki teaches the steps of: a) contacting a plurality of cells susceptible to caspase 3 induction with a virus from a first formulation; and b) measuring caspase 3 activity. Thus, the issue is does Banki teach repeating steps a) and b), with said virus being taken from said formulation at two or more time intervals.

We initially note that our mandate is to give claims their broadest reasonable interpretation. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). "An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." *In re Zletz*, 893

F.2d 319, 322 (Fed. Cir. 1989). Thus, as claim 1 does not specify any time interval, it only excludes when the two contacting steps, *i.e.*, step a) and the repeat of step a), are performed simultaneously. In other words, if any time elapses between the first time the cells are contacted with the virus and the second time the cells are contacted with the virus, it meets the requirement of said virus being taken from said formulation at two or more time intervals.

Banki, as noted above teaches that the data represented the mean of four or more independent experiments. Banki is silent on the timing of the experiments, but one of ordinary skill in the art would read the statement of Banki of performing independent experiments as excluding the situation where the experiments are started simultaneously. Thus, if the second experiment were started after the first experiment, and the third started after the second, and so on, that would meet the limitation of the virus being taken from said formulation at two or more time intervals. Thus, Banki teaches all of the limitations of the assay of claim 1.

Appellant argues that Banki fails to teach repeating both steps (a) and (b) (Br. 11). According to Appellant, Banki "describes a continuous time-course for measuring HIV induced apoptosis," and "does not appear to repeat the cell infection step using HIV obtained from a first formulation at different times." (*Id.*) According to Appellant, the fact that Banki referred to determining a mean variation using four experiments, does not mean that the virus was taken from the first formulation at different times (Reply Br. 3). Appellant asserts that all four experiments could have been performed at the same time, thus reducing any storage effects on the virus (*id.* at 3).

Appellant argues further that the rejection fails to identify the formulation used by Banki (Reply Br. 2).

As noted above, Banki teaches that the four or more experiments used to generate the data represented in panels (E) and (F) of Figure 2 were performed independently, which the ordinary artisan would read as excluding performing the experiments simultaneously. Moreover, performing the experiments sequentially would meet the limitation of said virus being taken from said formulation at two or more time intervals, and would also alleviate the need for storage of the virus.

In addition, Banki specifically teaches that the formulation of virus used was HIV-1 DNA clone 4803.

Claims 4, 5, 18, 19, 21, and 24 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Banki and Duncan.

Banki is relied upon as applied in the rejection of claims 1-3 and 7 under 35 U.S.C. § 102(b). In particular, according to the Examiner, Banki teaches the measurement of caspase 3 activity to quantify viral induced apoptosis (Answer 7).

Duncan is cited for teaching that the rubella virus induces apoptosis in Vero and RK13 cells (Answer 6). Duncan, according to the Examiner, quantified Rubella induced apoptosis by quantifying the number of detached cells (*id.*). The Examiner notes that Duncan "does not teach the measurement of caspase 3 activity as an alternative procedure to quantify virally induced apoptosis." (*Id.*)

The Examiner concludes:

> Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Banki [ ] with Duncan [ ]. One of ordinary skill in the art at the time the invention was made would have been motivated to so to quantify virally induced apoptosis. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of caspase 3 activity to quantify virally induced apoptosis is well known in the art.

(*Id.* at 7.)

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

Appellant argues[1] that the "proposal to modify Duncan" and measure caspase 3 activity as an indication of viral activity is inconsistent with Duncan's "looking for effects caused by apoptosis in general." (Br. 13.) Appellant asserts that Duncan is not concerned with measuring viral activity, and that Duncan also indicates that other caspases, in addition to caspase 3,

[1] Appellant argues the claims in three separate groups, with the first group comprising claims 4, 5, and 21, the second group comprising claims 18 and 19, and the third group comprising claim 24 (Br. 12-13; Reply Br. 4-5). As the arguments made by Appellant as to the first two groups are essentially the same, we need not address the first and second groups separately.

are involved in apoptosis (*id.*). According to Appellant, Banki "measures caspase 3 activity to study HIV induced apoptosis," and thus "fails to provide motivation to modify Duncan [ ] to specifically look at caspase 3 activity alone or in combination with other particular caspases, as an indication of viral activity." (*Id.*)

As noted by the Examiner, Banki teaches an assay for caspase 3 in looking at HIV induced apoptosis. Duncan also looks at viral induced apoptosis, specifically, rubella-virus induced apoptosis. Moreover, Duncan, in fact, looked at caspase activity in rubella-virus induced apoptosis (Duncan, p. 122, second column). Duncan cultured virus infected cells with an irreversible caspase inhibitor, which resulted in a decrease in the level of apoptosis (*id.*). As caspase 3 is one of the major group of effector caspases (see BACKGROUND section, above), it would have been obvious to one of ordinary skill in the art at the time of invention to assay for caspase 3 activity of rubella virus using the caspase 3 assay of Banki because Duncan specifically teaches that Rubella induces apoptosis. Note that measuring apoptosis is inherently measuring viral activity as it is the activity of the virus that results in apoptosis.

The fact that Duncan may be looking for effects caused by apoptosis in general, or that Banki only looks at capsase 3 activity in regard to HIV infection, does not render the combination improper. "[T]he analysis need not seek out precise teachings directed to the specific subject matter of the . . . claim," as "the inferences and creative steps that a person of ordinary skill in the art would employ" may be taken into account. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

As to claim 24, Appellant asserts that Banki is cited for teaching HIV and Duncan is cited for using rubella (Reply Br. 5). Appellant argues that the Examiner "fails to indicate where the combination of Banki [ ] and Duncan [ ] provides for using either measles or mumps." (*Id.*)

We agree, and are thus compelled to reverse the rejection of claim 24 as being rendered obvious by the combination of Banki and Duncan. We do address claim 24 in the rejection based on the combination of Banki and Esolen.

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Banki and Wu.

Banki is relied upon as applied in the rejection of claims 1-3 and 7 under 35 U.S.C. § 102(b). The Examiner notes that while Banki teaches "storing aliquots of supernatants with viral titers by freezing the aliquots at -70 degrees C," it is unclear if Banki lyophilized the virus (Answer 7).

Wu is cited for teaching that "lyophilization improves the stability of viral vaccine and recombinant protein products." (*Id.*)

According to the Examiner,

> it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to lyophilize the virus. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to improve the stability of the viral supernatant. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the art recognizes that lyophilization improves the stability of viral vaccine and recombinant protein products. Thus, absent evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for producing the claimed invention.

(*Id.* at 7-8.)

Appellant merely reiterates his arguments as to claim 1 and Banki, also asserting that Wu fails to cure the deficiencies of Banki (Br. 14). These arguments are not persuasive for the reasons set forth above with respect to the rejection of claims 1-3 and 7 under 35 U.S.C. § 102(b) as being anticipated by Banki. Thus, this rejection is affirmed.

Claim 8 stands rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Banki and Goodrich.

Banki is relied upon as applied in the rejection of claims 1-3 and 7 under 35 U.S.C. § 102(b). The Examiner notes that Banki "does not teach the freezing and thawing of the cells prior to contacting the cells with the virus." (Answer 8.)

Goodrich is cited for teaching a method of storing cells by freezing, and later thawing the cells for use (*id.*).

The Examiner concludes

> it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to freeze and thaw the cell. One of ordinary skill in the art at the time the invention was made would have been motivated to freeze the cells to allow storage of the cells, and thaw the frozen cells to use the cells. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the freezing and thawing of cells is well recognized in the art as a method of storing cells. Thus, absent evidence to the contrary, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for producing the claimed invention.

(*Id.* at 8-9.)

Appellant merely reiterates his arguments as to claim 1 and Banki, also asserting that Goodrich fails to cure the deficiencies of Banki (Br. 14). These arguments are not persuasive for the reasons set forth above with respect to the rejection of claims 1-3 and 7 under 35 U.S.C. § 102(b) as being anticipated by Banki. Thus, this rejection is affirmed.

Claims 22 stands rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Banki and Esolen.

Banki is relied upon for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis (Answer 9). The Examiner notes that Banki does not teach measurement of caspase 3 activity induced by measles (*id.*).

Esolen is cited for teaching that the measles virus induces apoptosis.

Thus, the Examiner concludes that

> it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to combine the teachings of Banki [ ] and Esolen [ ]. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to quantify apoptosis induced by the measles virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because the use of caspase 3 activity to quantify virally induced apoptosis is well known in the art.

(*Id.*)

Appellant argues that Esolen is not concerned with determining viral activity, but is instead directed to determining the mechanisms of measles virus-induced cell death (Br. 15). According to Appellant, Esolen "does not

reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified," thus one of ordinary skill would not have been motivated to combine Esolen with Banki (*id.*).

As noted by the Examiner, Banki teaches an assay for caspase 3 in looking at HIV induced apoptosis. Esolen is also directed to viral induced apoptosis, specifically, measles virus induced apoptosis. As caspases are known to be involved with cellular apoptosis, and as caspase 3 is one of the major group of effector caspases (see BACKGROUND section, above), it would have been obvious to one of ordinary skill in the art at the time of invention to assay for caspase 3 activity of measles virus using the caspase 3 assay of Banki because Esolen specifically teaches that measles induces apoptosis. Note that measuring apoptosis is inherently measuring viral activity as it is the activity of the virus that results in apoptosis and cell death. The fact that Esolen may be directed to determining the mechanisms of measles virus-induced cell death does not render the combination improper. *KSR,* 127 S. Ct. at 1741.

We note that claim 24 should have been included in this rejection, as Esolen teaches the measles virus. Thus, we also apply this rejection to claim 24. This is a new ground of rejection.

Claims 1, 20, 23, and 25 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Banki, Duncan, and Wu.

The Examiner references the teachings of Banki or Banki as combined with Duncan as already discussed above (Answer 10). According to the Examiner, Banki teaches a method of measuring caspase 3 activity to

quantify virally induced apoptosis, but fails to teach measuring caspase 3 activity induced by the virus obtained from two different formulations (*id.*).

Wu is cited for teaching the significance of formulations on the biological activity and structural integrity of viral particles (*id.*).

According to the Examiner,

> it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to compare different viral formulations. One of ordinary skill in the art at the time the invention was made would have been motivated to do so to determine the effects of the formulation on the biological activity and structural integrity of the virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because Banki [ ] teaches the measurement of caspase 3 activity to quantify virally induced apoptosis.

(*Id.*)

As to claims 1 and 25, Appellant argues that the "fact that formulations can affect viral activity, does not provide motivation to measure caspase 3 activity as an indication of viral activity in different formulations." (Br. 16.) Banki, Appellant asserts, "does not indicate that caspase 3 should be measured to provide an indication of viral activity in comparing formulations," and Wu's teachings "on the significance of formulations on biological activity fail to cure such deficiencies." (*Id.*)

While Banki does not specifically look at different formulations of the HIV virus, the reference does look at the activity in two different cell types, H9 and Jurkat-tat (Banki, Figure 2). Given Wu's teaching of the significance of formulations on the biological activity and structural integrity of viral particles, it would have been obvious to one of ordinary

skill in the art to look at apoptosis and caspase 3 activity of different viral formulations.

Claim 20 is further distinguished, according to Appellant, as it requires that the virus be measles, mumps, or rubella (Br. 16). Claim 23, Appellant argues, further limits the virus to mumps or rubella (*id.*).

Appellant's arguments are not convincing, as Banki as combined with Duncan teaches assaying for caspase 3 activity in rubella as a measure of viral activity.

CONCLUSION

In summary, we affirm the Examiner's rejection of claims 1-8, 18-23, and 25. We reverse the Examiner's rejection of claim 24, but enter a new ground of rejection of claim 24 under 35 U.S.C. § 103.

TIME PERIOD FOR RESPONSE

Regarding the affirmed rejection(s), 37 CFR § 41.52(a)(1) provides that "Appellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the examiner's rejection(s) of one or more claims, this decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the Appellant elect to prosecute further before the Examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the Examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the Appellant elect prosecution before the Examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED; 37 C.F.R. § 41.50(b)

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